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PROVISIONAL SPECIFICATION

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Invention Title: **Natural health supplement.**

The invention is described in the following statement:

5014

NATURAL HEALTH SUPPLEMENT

This invention relates to natural products containing phyto-oestrogens, or phyto-oestrogen metabolites, which have various beneficial physiological effects in man and other animals, and which have a variety of uses, such as to promote good health and as a dietary additive, for example.

The particular product in accordance with the invention is composed of various nutrients and chemicals, some that are important (e.g. protein, fat, carbohydrate, vitamins, minerals) and others that have little or no known nutritional value to animals and man. However, the important component in relation to the present invention are the phyto-oestrogens, or their closely related derivatives and metabolites. Phyto-oestrogens are hormones which play important roles in plant reproduction, mediating such activities as flowering and budding. Because of their functional importance, it is reasonable to expect that they may be present in all plants, although at present their presence has been sought in a limited number of plant types only, and they have been found to be present in variable but detectable levels in those plants.

There are different types of phyto-oestrogens as follows:

Type 1 phyto-oestrogens - these are compounds closely related to animal oestrogens such as oestrone, oestradiol and oestriol. They have been described in plants such as liquorice (Glycyrrhiza glabrata), apple (Malus sylvestris), French bean (Phaseolus vulgaris), pomegranate (Punica granatum), and date palm (Phoenix dactylifera).

Type 2 phyto-oestrogens - coumestans. A large number of coumestans have been isolated, but only a small number show oestrogenic activity in animals. The important ones occur in alfalfa (Medicago sativa), ladino clover (Trifolium spp.) and some other fodder crops such as barrel medic

(Medicago litteralis) where they have important effects on the reproductive performance of grazing animals. In human diet, the important sources of coumestans are sprouts of soya (Soja max) and alfalfa (Medicago sativa) where levels up to 7 mg/100 gm dry weight are seen. Whole soyabeans contain levels of approx. 120 mg/100 gm dry weight and most of that is concentrated in the seed hull.

Type 3 phyto-oestrogens - resorcylic lactones. These are compounds which are not intrinsic components of plants but are metabolites of fungal infections (particularly Fusarium spp.) associated with plants. They principally affect fodder crops where they may be significant in the health of grazing animals. Resorcylic lactones have been isolated in such foodstuffs as oats (Avena sativum), barley (Hordeum volgare), corn (Zea mays) and rice (Oryza sativa) which feature in human diets.

Type 4 phyto-oestrogens - isoflavones. These have only been isolated in significant quantities from leguminous plants such as soya (Soya max), chick pea (Cicer arietinum), and clovers (Trifolium spp.).

Phyto-oestrogens of Types 1 and 3 above generally occur at comparatively low levels in most human diets and are considered to have little, if any, significance in terms of human and animal nutrition. In contrast, coumestans, and to a greater extent, isoflavones, are far more prominent in the human diet and for that reason are thought to have some significance to human nutrition.

It is known that dietary phyto-oestrogens are absorbed by animals (including man) from the gut, then circulate in blood, and are excreted in the urine and bile. A proportion of the phyto-oestrogens are absorbed in a relatively unchanged form, while a further proportion undergo bacterial fermentation in the gut to produce a range of metabolites which are then absorbed.

Phyto-oestrogens have been shown to have a range of biological effects in animals in vivo or on animal tissues in vitro. Those effects include anti-carcinogenicity, and

anti-fungal and anti-bacterial activities. However, the potentially most significant biological effect of in animals is related to the oestrogenicity of some of the phyto-oestrogens and some of their metabolites. Some phyto-oestrogens, in particular coumestans and isoflavones, closely resemble structurally animal oestrogens and are able to mimic the activities of those animal oestrogens when injected into animals. However, while they do display oestrogenicity in animals, that effect is substantially weaker than that of the animal oestrogens. But experimental evidence indicates that the more significant biological effect of these compounds is their ability to compete with natural animal oestrogens for the oestrogen receptors on the surface of cells.

In the body, naturally-occurring oestrogens circulating in the blood exert their activity by interaction with oestrogen receptors on cell surfaces; such interaction then triggering a particular biological function of that particular cell. However, phyto-oestrogens also are able to bind to those oestrogen receptors because the structure of these compound so closely resembles the animal's own oestrogens, but unlike the animal oestrogens, phyto-oestrogens only weakly activate the oestrogen receptor.

It is likely that natural oestrogens and phyto-oestrogens compete equally for those binding sites, so in this way, the phyto-oestrogens are inhibiting the effect of oestrogens and can be considered to have an anti-oestrogenic effect. This phenomenon is known as competitive-inhibition, by which is meant that the biological effect of an active substance is impaired by the competitive binding to a target receptor of a similar but inactive compound.

At high levels, dietary phyto-oestrogens can have a profound physiological effect in animals causing severe reproductive dysfunction. An example of this is sheep grazing pastures containing certain strains of subterranean clover which can contain levels of phyto-oestrogens as high

over

as 5% of the dry weight of the plant. As a result of the competitive-inhibitory effect of these phyto-oestrogens on oestrogen function in the hypothalamus, both male and female sheep develop adrogenic symptoms.

Such high dietary levels of phyto-oestrogens, however, are rare. It is far more common that many animal and human diets contain just moderate levels of phyto-oestrogens and there is some evidence to support the view that moderate levels have a beneficial effect on health. In the human diet, dietary phyto-oestrogens come predominantly from legumes.

Legumes are by definition those plants that have the capability of fixing atmospheric nitrogen and for that reason yield seeds and fruit with high protein content. Coincidentally, they also appear to have relatively higher levels of phyto-oestrogens (particularly isoflavones) than do other plant types. Soya is a particularly rich source of phyto-oestrogens, containing approximately 300-1500 mg of isoflavones per 100 gm of whole soya, with the content varying according to factors such as strain variety and seasonal and growing conditions. Other common dietary legumes such as lentils, chickpeas and beans generally contain lower levels than those in soya, but still have much higher levels than that found in non-leguminous plants.

Legumes (also known as pulses) play an important dietary role in many traditional human cultures. In those cultures, the legume serves as a cheap and relatively abundant source of protein and fats. Hence, soya is a staple in Asia, beans (broad, haricot, kidney, lima, navy etc) are staples in South America, and chickpeas and lentils are staples in India and Mediterranean countries. In more affluent countries, whereas legumes (dried nuts, peas and beans) were a major source of protein up to the end of the 19th century, legume consumption has over the last 100 years declined significantly, having been replaced in the diet with protein of animal origin.

dietary phyto-oestrogens may therefore be expected to lead to an imbalance in the levels of different oestrogens and/or the effects of those oestrogens in the body.

It is also possible that the relatively higher levels of phyto-oestrogens in the diets of traditional cultures in such developing regions as South-East Asia, India, South America and the Mediterranean which incorporate larger amounts of legumes compared to the standard diets in most developed countries, may in part account for the traditionally lower incidence in developing countries of diseases such as cancer of the breast, cancer of the bowel, cancer of the uterus, cancer of the prostate, athero-sclerosis, pre-menstrual syndrome, and menopausal syndrome, all of which are related to oestrogen metabolism to varying degrees.

To that end, the inclusion of greater levels of legumes (particularly those rich in phyto-oestrogens such as soya, chickpeas and lentils) in the standard diets of developed countries could be expected to redress a general oestrogenic imbalance in both men and women in developed countries thereby reducing the predisposition of those communities to the above diseases.

However, it is unrealistic to expect that public education programmes would readily convert communities in developed countries from a diet where the protein content is predominantly animal-derived, to one where the protein is predominantly legume-derived. An alternative strategy is to make available either (i) phyto-oestrogens in a purified form or (ii) foodstuffs which are enriched for phyto-oestrogens. In this way, the phyto-oestrogens could be added to the diet in a convenient form as a supplement without requiring any substantive change to the diet.

In soya, the coumestan content is contained principally in the hull and hypocotyl of the whole soyabean; the two cotyledons which represent the bulk (90% by weight) of the soyabean contain only minimal levels of coumestans. Similarly, isoflavones occur principally in the hypocotyl,

The current general consumption rates (gm/day/person) for legumes for different regions are currently approximately: Japan (90), India (50), South America (20-60), North Africa (50), Central/Southern Africa (20-50), Northern and Southern Mediterranean (20-30), Western Europe/North America/Australasia (5-15).

Thus people belonging to cultures in which legumes play an important dietary role are consuming on a daily basis significant quantities of phyto-oestrogens. Conversely, most Western developed countries currently generally have negligible to low dietary phyto-oestrogen levels because of the low level of dietary legumes, although this is a relatively recent phenomenon since up to the end of the 19th century legumes continued to be an important, albeit declining, part of the diet for the majority of the populations in Europe and North America.

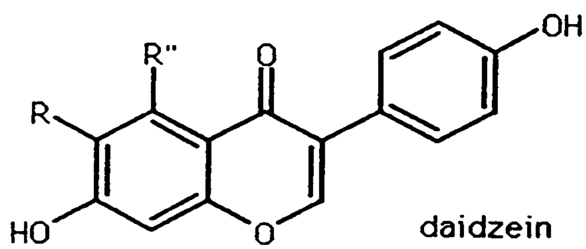
It is thought that legumes have played an important part of the human diet over the past 20,000-30,000 years. It therefore follows that human metabolism have probably evolved and developed over this time in the presence of relatively large levels of dietary phyto-oestrogens, particularly isoflavones. Given the known biological effects of phyto-oestrogens, it also follows that endogenous oestrogen metabolism and function has evolved in the face of a significant competitive-inhibiting effect by phyto-oestrogens. Clinical evidence now indicates that a relative deficiency of dietary phyto-oestrogens leads to an imbalance of normal oestrogen metabolism and function in animals, including man.

It is possible that the inclusion of phyto-oestrogens such as coumestans and isoflavones in human diet during recent human evolution has resulted in some sort of adaptation of the oestrogenic metabolism in humans to the presence of these compounds. That is, both the rate of production and the function of oestrogens may be either dependent upon or influenced by the presence of phyto-oestrogens in the body. A relative deficiency of

with the cotyledons containing much lower amounts. As the hull and hypocotyl represent just a small proportion by weight (8% and 2% respectively) of the entire soyabean, it can be seen that the phyto-oestrogens are concentrated in these two structures of the bean.

The hull and hypocotyl can be removed from whole soya beans by physical means, allowing them to separate from the cotyledons. The hulls and the hypocotyls can subsequently be separated from each other by physical means based on the higher density and smaller size of the hypocotyls.

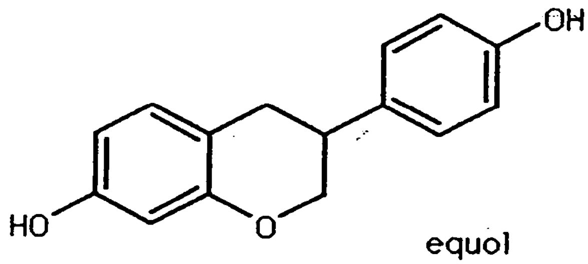
There is a further advantage in using the hypocotyl as a source of isoflavones compared to the whole soya bean, because of the relative incidences of the different isoflavones in the hypocotyl compared with the cotyledon. The isoflavone content in soy ranges from about 0.047% to 0.36% by weight. Three principal isoflavones have been identified - they are glycitein, genistein and daidzein. In plants these compounds occur principally as glycosides (glycitin, genistin, daidzin) with a smaller proportion present as aglucones (glycitein, genistein, daidzein).



daidzein R = H, R" = H
genistein R = H, R" = OH
glycitein R = OCH_3, R" = H

Following ingestion by animals, the isoflavones are hydrolysed to the free form. A small amount of these then are absorbed directly from the bowel and circulate in the blood. The bulk of the isoflavones remaining in the bowel, however, undergo fermentation by bowel bacteria to form various metabolites. These metabolites then are absorbed into the blood stream. Of the different isoflavones,

glycitein and its metabolites have negligible oestrogenic activity; genistein is oestrogenic, but its principal metabolites (para-ethylphenol and O-desmethylangolensin) have negligible oestrogenic activity; daidzein is oestrogenic, and it has two principal metabolites - O-desmethylangolensin and equol. Equol is strongly oestrogenic, being some 100 times more potent in this respect than the parent daidzein compound, or than genistein.



equol

It is therefore likely that equol is the principal source of the oestrogenic and anti-oestrogenic activity of isoflavones. In soya beans, the genistein is located predominantly in the cotyledons, while daidzein occurs predominantly in the hypocotyl.

The opportunity then exists to formulate a food supplement based on soya hulls only (as an enriched source of coumestans), or soya hypocotyls only (as an enriched source of isoflavones and moderate levels of coumestans), or a mixture of soya hulls and soya hypocotyls (as an enriched source of both coumestans and isoflavones). Similarly, these materials may be used as a source of coumestans and isoflavones for further chemical or physical extraction or purification of those compounds leading to the further enrichment or eventual purification of these compounds for the purposes listed above.

However, a preferred embodiment of the present invention is a blend of soya hulls and soya hypocotyls (in which the soya hull content of the final blend varies between 0.1% and 99.9%) without further steps to enrich the phyto-oestrogens. Such a product offers the further advantage of being a rich source of dietary soluble fibre

which is generally considered to have a beneficial effect to human health.

Soya hypocotyls compared to whole soya beans or any other whole form of legume, offer distinct advantages (i) as an enriched source of isoflavone (1.5% vs 0.3% w/w), and (ii) as a source of a proportionately greater amount of the more desirable isoflavone, daidzein.

While soya is the preferred source of phyto-oestrogens, other sources can be utilized in the invention. Soya is a preferred source of coumestan and isoflavone because of (a) the ready availability of large quantities of this material, (b) the high proportion of daidzein relative to genistein in the hypocotyl, (c) the relative ease in the separation and collection of hulls and hypocotyls, and (d) the high levels of both coumestans and isoflavones.

An alternative source of these isoflavones is subterranean clover (Trifolium spp.), many varieties of which have isoflavone levels of the order of 5% of dry weight. Compared to soya, however subterranean clovers are less advantageous because of the relative absence of coumestans.

However, other leguminous plants as detailed here could be used as sources of isoflavones and coumestans: Indian liquorice (Abrus precatorius); various species of Acacia spp. including A. aneura, A. cibaria, A. longifolia, and A. oswaldii; ground nut (Apio tuberosa); ground pea (Arachis hypogea); milk vetch (Astragalus edulis); marama bean (Bauhinia esculenta); sword bean (Cajanus cajan indicus); jack bean (Canavalia ensiformis); sword bean (Canavalia gladiata); seaside sword bean (Canavalia rosea); various Cassia spp. including C. floribunda, C. laevigata, and C. occidentalis; carobbean (Ceratonia siliqua); chick pea (Cicer arietinum); yebnut (Cordeauxia edulis); various Crotalaria spp. including C. laburnifolia, and C. pallida; cluster bean (Cyamopsis psoralioides); tallow tree (Detariaum senegalense); sword bean (Entada scandens); balu (Erythrina edulis); soyabean (Clycine max;) inga (Inga

edulis); Polynesian chestnut (Inocarpus fagifer); hyacinth bean (Lablab purpureus); grass pea or Indian vetch (Lathyrus sativus); cyprus vetch (Lathyrus ochrus); lentil (Lens culinaris); jumping bean (Leucaenal eucocephala); various Lupinus spp. including L. albus, L. luteus, L. angustifolium, L. mutabilis, and L. cosentinii; ground bean (Macotylma geocarpa); horse gram (Macrotyloma uniflorum); alfalfa (Medicago sativa); velvet bean (Mucuna pruriens); yam beans (Pachyrhyzuz erosus, P. tuberosus); African locust bean (Parkia clappertoniana); Parkia speciosa; oil bean tree (Pentaclethra macrophylla); various Phaseolus spp. including P. acutifolius, P. vulgaris, P. luntus, P. coccineus, P. adenathus, P. angulris, P. aureus, P. calcaratus, P. mungo, and P. polystachyus; garden pea (Pisum sativum); djenko bean (Pithecolobium lobatum); mesquite (various Prosopis spp.); goa bean (Psophocarpus scandens, P. tetragonolobus); various Psoralea spp.; Sesbania bispinosa; yam bean (Sphenostylis stenocarpa); tamarind (Tamarindus indica); fenugreek (Trigonella foenum-graecum); vetches (various Vivia spp. including V. sativa, V. atropurpurea, V. ervilia, and V. monantha); broad bean (Vicia faba); black gram (Vigna mungo); various Vigna spp. including V. radiata, V. aconitifolia, V. adanatha, V. angularus, V. tribolata, V. umbelata, and V. unguiculata; and, earth pea (Voandzeia subterranea).

Soya hypocotyls may be used as an enriched source of isoflavones and coumestans (0.5-1.5% dry weight) with or without the presence of additional soya hulls. Alternatively, other sources can be utilized, as listed above. This can be consumed either in the raw form (eg, natural hypocotyls), or the hypocotyls (with or without soya hulls) can be ground or milled to a powder or flour which can be used as a dietary supplement in a variety of ways including, for example, as a powder, in a liquid form, in tablet form, or added to other prepared foodstuffs. Herbal and similar types of health food and dietary supplements that include these phyto-oestrogens can also be prepared.

Equol, which is metabolized from daidzein, itself seems to be a dietary substance essential to the proper functioning of the human body, or in other words, equol (or daidzein) may be a new natural "vitamin".

The invention also includes the possibility of processing further the soy or other produce containing concentrated isoflavones and daidzein to further concentrate, or even isolate the daidzein, and if desired, to convert it into equol, for use as a new vitamin. Equol is also capable of being synthesised.

The concentrated or purified daidzein, or concentrated or pure equol can be compounded as a vitamin, in tablet, capsule, liquid or similar form, or incorporated in food as an additive, for example.

The product of the invention modulates the production and/or function of endogenous sex hormones in humans and other animals to modify or produce the following effects: (i) lowered levels of blood lipoproteins including low-density and very-low-density cholesterol leading to reduced risk of development of atherosclerosis; (ii) reduced risk of development of cancer of the prostate; (iii) reduced risk of cancer of the breast; (iv) reduced risk of development of cancer of the uterus; (v) reduced risk of cancer of development of cancer of the large bowel; (vi) reduced risk of development of the syndrome in women commonly referred to pre-menstrual tension; (vii) reduced risk of development of many untoward symptoms (including dry vagina, peripheral flushing, depression etc) commonly associated in women with menopause. These and other complaints and diseases can be prevented or ameliorated in accordance with the invention.

The invention is therefore directed to a method for the prophylaxis or treatment of an animal, including a human, to combat conditions associated with phyto-oestrogen deficiency, which comprises administering to the animal an effective amount of phyto-oestrogen selected from the

isoflavones and/or the coumestans, ideally in concentrated form.

Preferably the phyto-oestrogens are derived from, or the phyto-oestrogen source comprises, the hull and/or hypocotyl of soyabean. However plants, other than soya, which contain significant amounts of isoflavones or coumestans can be used. Preferably also, the isoflavones are selected from a source rich in daidzein or genistein, most preferably daidzein, or their metabolites or derivatives. Particularly preferred is to use a product particularly rich in daidzein or its metabolite equol.

The invention also concerns formulations containing phyto-oestrogens selected from the isoflavones and/or coumestans. Such formulations containing the hull and/or hypocotyl of soyabeans are particularly preferred. Also preferred are formulations containing the isoflavones daidzein or genistein or their metabolites, or derivatives, especially equol.

The formulations may be a variety of kinds, such as nutritional supplements, pharmaceutical or veterinarial preparations, vitamin supplements, food additives or foods supplemented with the active phyto-oestrogens of the invention, liquid or solid preparations, including drinks, sterile injectable solutions, tablets, coated tablets, capsules, powders, drops, suspensions, or syrups, ointments, lotions, creams, pastes, gels, or the like. The formulations may be in convenient dosage forms, and may also include other active ingredients, and/or may contain conventional excipients, carriers and diluents. The inclusion of the subject phyto-oestrogens in herbal remedies and treatments is also a preferred part of the invention.

The invention is also directed to the amelioration, prevention, or of various conditions responsive to treatment with the phyto-oestrogen substances of the invention.

The invention is now described with reference to various examples.

Example 1 - preparation of soy phyto-oestrogen product. Soybeans were processed through a separation mill. Firstly, the beans are heated, so that the husk becomes brittle, then the mill removes the husk and splits the bean into the two cotyledons and the small-sized hypocotyl which separate from each other. Normal soybean separation mills discard the husks, and also separate and remove the small hypocotyl which can impart a bitter taste to the oil and soy-flour product from the soybeans.

For the purpose of the present invention these two "waste" products are collected separately, and optionally are processed further; for example by turning the husks and/or hypocotyl to a fine powder.

Further common processing steps can be used, if desired, to convert the husk or hypocotyl natural product or powder to capsule, tablet, liquid similar convenient form for ingestion. Otherwise the powder can be packaged as a convenient food additive or condiment, as occurs for other herbs and spices.

Example 2 - Effect of administering phyto-oestrogens to humans.

Tablets were prepared comprising 400 mg of whole soygerm (soy hypocotyls), and each tablet contained approximately 45 mg of isoflavones.

Two such tablets were taken daily by 18 volunteers for a period of 2 months. The effects of administering the soy phyto-oestrogen concentrate on blood cholesterol was determined by comparing the blood cholesterol levels in the volunteers before and after the experiment, with the levels of equol in urine.

Equol is the final metabolic product of one of the isoflavones, namely daidzein, in the body, and there is no other source of equol known other than from the metabolic reaction of daidzein. Therefore the presence of equol is directly the result of the soygerm tablets.

The results of the experiment are shown in the following Table. The total cholesterol is expressed as

mmol/litre and the equol level is expressed as mg per 24 hour urine volume. The results are presented as a range with the mean value shown in brackets. The individuals are grouped according to their ability to produce equol, in order to demonstrate the effects of administering the concentrated soy isoflavones.

	Pretreatment		Post-treatment	
Groups	Total cholesterol	Urinary equol	Total cholesterol	Urinary equol
Group 1 (n=7)	6.3-7.8 (7.2)	0-0.01 (0)	5.0-6.1 (5.6)	0.1-1.3 (0.9)
Group 2 (n=6)	5.0-6.2 (5.4)	0-0.01 (0)	44-5.3 (4.9)	0.3-2.4 (1.6)
Group 3 (N=5)	3.5-4.8 (4.0)	0-0.02 (0.01)	3.4-4.9 (4.0)	1.5-12.8 (6.8)

The pretreatment levels show that the average western diet contains little or no isoflavone, because of the very low amount of equol present. After the two months of treatment, appreciable equol levels are detected.

The results provide support for the ability of soygerm to lower blood cholesterol levels, due to the strong inverse correlation between an individual's baseline blood cholesterol level and the ability to metabolise daidzein to equol. That is, the greater is the person's ability to metabolise equol, then the lower is the cholesterol level.

The Table indicates that individuals with low baseline cholesterol levels and who are very efficient metabolizers of daidzein to equol, who make up Group 3, are likely to be obtaining sufficient dietary isoflavone to control their cholesterol, even though the amount of isoflavone they may be obtaining is small. As a result they show no response to their extra soygerm intake, in terms of the further lowering of either cholesterol levels. Whereas, those individuals in Groups 1 and 2 who have relatively less metabolic efficiency

in converting daidzein to equol, will respond to the additional dietary daidzein intake, with their cholesterol levels falling significantly.

Example 3 - Nutritional supplement products

(a) Finely ground soy hypocotyls is combined with Silybum marianum, vitamin B3 nicotinic acid) and Dandelion, to produce a natural health product to assist in controlling and lowering cholesterol levels in humans.

(b) Finely ground soy hypocotyls and husk is combined with some or all of the following herbs and vitamins, to prepare a natural health product for treating menopause: Dong quai, Vitex agnus castus, Sage, and Vitamin E.

(c) Finely ground soy hypocotyls and husk is combined with some or all of the following herbs and vitamins, to prepare a natural health product for treating pre-menstrual tension (PMT) and period problems in women: Black Haw, Dong quai, Vitex agnus castus, Calcium, Magnesium, B group vitamins, Vitamin E and Folic acid.

(d) Finely ground soy hypocotyls and husk is combined with some or all of the following herbs and vitamins, to prepare a natural health product for treating cancer: Betacarotene, Vitamin C, Vitamin E, Silybum marianum, Ginkgo and Bioflavonoids.

DATED this 19th day of May, 1992.

GRAHAM EDMUND KELLY
By His Patent Attorneys
DAVIES COLLISON CAVE

0446e/VMJ